Adding ribavirin to interferon α-2b for chronic hepatitis C infection increased virological response and nausea

Reichard O, Norkrans G, Frydén A, et al for the Swedish Study Group. **Randomised, double-blind, placebo-controlled trial of interferon α-2b with and without ribavirin for chronic hepatitis C.** *Lancet 1998 Jan 10;***351***:83–7.*

Question
In patients with chronic hepatitis C virus (HCV) infection, is the addition of ribavirin to interferon α-2b effective and safe?

Design
48 week randomised, double blind, placebo controlled trial.

Setting
5 university hospitals in Sweden.

Patients
100 patients (mean age 40 y, 62% men) who had increased aminotransferase concentrations for ⩾6 months, serum antibodies to HCV found by polymerase chain reaction (PCR), and a diagnosis of chronic hepatitis on a liver biopsy sample in the previous 12 months. Exclusion criteria included previous treatment with interferon α-2b or ribavirin, decompensated cirrhosis, autoimmune hepatitis, chronic hepatitis B infection, HIV infection, current intravenous drug use, liver disease related to drug use, or pregnancy.

Intervention
Patients were allocated to combination therapy (subcutaneous interferon α-2b, 3 MU three times/wk, plus ribavirin, 1000 mg daily in 2 divided doses) (n=50) or monotherapy (subcutaneous interferon α-2b plus a matching placebo) (n=50) for 24 weeks. Patients who weighed ⩾75 kg received 1200 mg of ribavirin. 90% of patients completed 24 weeks of treatment.

Main outcome measures
Virological sustained response (absence of HCV RNA on PCR at weeks 24 and 48). Secondary outcomes were biochemical and histological responses and safety outcomes.

Main results
Analysis was by intention to treat. More patients allocated to combination therapy than to monotherapy had a virological sustained response (p=0.047) (table). Combination therapy led to more patients with nausea (p=0.02) needing a dose reduction or discontinuing treatment than did monotherapy (p=0.03) (table). No differences existed between groups for histological improvement.

Conclusion
In patients with chronic hepatitis C infection, the addition of ribavirin to interferon α-2b led to an increase in sustained virological response but also to more dose reductions or treatment withdrawals and nausea.

*Interferon α-2b plus ribavirin (combination therapy) v interferon α-2b alone (monotherapy) at 48 weeks in chronic hepatitis C virus infection**

Outcome	*Combination therapy*	*Mono-therapy*	*RBI (95% CI)*	*NNT (CI)*
Virological response	36%	18%	100% (2 to 302)	6 (3 to 193)
Outcomes	Combination therapy	Mono-therapy	RRI (CI)	NNH (CI)
Dose reduction or treatment withdrawal	32%	12%	167% (19 to 520)	5 (3 to 27)
Nausea	34%	12%	183% (27 to 555)	5 (3 to 18)

*RBI=proportional increase in rates of good outcomes between combination therapy and monotherapy groups; NNT=number of patients who must receive combination therapy to achieve 1 additional good outcome; RRI=proportional increase in rates of bad outcomes between combination therapy and monotherapy groups; NNH=number of patients who, if they received combination therapy, would lead to 1 additional person being harmed.

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Commentary

Treatment with α interferon is widely recommended for chronic hepatitis C.[1] However, the clinically relevant outcome of sustained response—that is, no HCV RNA in serum by PCR and normalisation of alanine aminotransferase (ALT) persisting after treatment for more than 6 months—is found in only about 15% of patients. Lower response rates are observed in patients with genotype 1, those with a high viral load, or cirrhosis at start of therapy.[2] Ribavirin is an oral nucleoside analogue that lowers serum ALT in chronic hepatitis C but its effect on HCV replication is minimal.

Reichard *et al* carried out a large, double blind, randomised controlled trial to assess the efficacy and safety of combination therapy with interferon and ribavirin. One hundred consecutive patients without previous treatment with interferon or ribavirin entered the trial and received either α interferon 3 MU three times weekly plus placebo daily, or interferon plus ribavirin 1–1.2 g daily for 24 weeks. Follow up lasted for another 24 weeks.

Significantly more patients on combination therapy (16/50) than on interferon monotherapy (6/50) needed a reduction in dose or discontinued treatment; depression, nausea and a decrease in haemoglobin were more common in the combination therapy group. A sustained response was seen in 18 (36%) patients on combination and in 9 (18%) on interferon monotherapy (p<0.05). Subgroup analysis indicated particularly enhanced efficacy of combination therapy in patients with a high viral load (⩾8 MEq/ml by bDNA, Chiron), whereas no effect could be shown in patients with genotype 1b.

This relatively large trial was designed and executed according to modern standards, and virological assays were of high quality. However, the number of patients inthe study was too small to allow subgroup analysis with confidence.

The potential clinical impact of the Swedish findings is that combination of interferon with ribavirin will be regarded as the treatment of choice for patients with chronic hepatitis C and an indication for antiviral treatment. However, the greater number of side effects and the considerably higher cost of combination therapy compared with interferon monotherapy will mean that this treatment will probably not be universally applied. Interferon monotherapy will suffice for 10–20% of patients, and additional subgroup analysis is needed to identify those individuals. Furthermore, many patients do not respond to combination treatment, which should be suspended if HCV RNA is detected after 12 weeks. Such a cost effective strategy, coupled with the now appreciable chance to eradicate the virus as suggested by long term follow up studies,[3] should widen the application of treatment in chronic hepatitis C.

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1 Anonymous. National Institutes of Health Consensus Development Conference Panel statement: management of hepatitis C. *Hepatology* 1997;**26**(suppl 1):2–10S.
2 Brouwer JT, Nevens F, Kleter B, *et al*. Efficacy of interferon dose and prediction of response in chronic hepatitis C: Benelux study in 336 patients. *J Hepatol* 1998;**28**:951–9.
3 Marcellin P, Boyer N, Gervais A, *et al*. Long-term histologic improvement and loss of detectable intrahepatic HCV RNA in patients with chronic hepatitis C and sustained response to interferon-alpha therapy. *Ann Intern Med* 1997;**127**:875–81.